

# Is there a link between the circulating renin-angiotensin system and coronary disease?

## A sceptical view

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Research on the renin-angiotensin system during the 20th century provides a history of the impact of scientific growth upon our understanding of pathophysiology. The techniques of experimental physiology, "classical" chemistry, biochemistry, and pathology have had a major impact which has been succeeded by the newer techniques of immunochemistry and molecular biology. Epidemiology and clinical trials methodology have also played critical roles. Patient wellbeing has been significantly advanced, initially by the development of diagnostic tests based upon this technology and latterly by the development of potent drugs which inhibit the renin-angiotensin system. In many ways it is remarkable that the relationship between the renin-angiotensin system and the most common cause of cardiovascular morbidity and mortality (that is, ischaemic heart disease) is still uncertain and controversial. It now cannot be denied that the renin-angiotensin system plays a significant role in cardiovascular disease. What remains uncertain is the mechanism and extent of the association, and to what extent the system has an impact upon cardiac disease independent of its well defined effects upon blood pressure. The purpose of this review is to make clear my grounds for scepticism about the current evidence.

### Types of evidence

Associations such as those described between plasma renin activity and coronary heart disease<sup>1</sup> could be the result of pathological effects of high circulating (or perhaps locally generated) angiotensin II concentrations. There are, however, two alternative explanations that cannot be excluded in such largely retrospective reports. High plasma renin activity could be a result of pre-existing vascular damage or the association could be due to unrecognised confounding factors which influence both plasma renin activity and the incidence of ischaemic heart disease. The demonstration of causality demands three types of evidence.

These are: (1) Biologically plausible mechanisms by which angiotensin II could give rise to coronary events; (2) the demonstration of specific associations in clinical and epidemiological studies (that is, an association which cannot be explained by any other factor); (3) reversal of the increased risk associated with high plasma renin activity by inhibition of the renin-angiotensin system. Further, such reversal of risk has to be specifically related to inhibition of the renin-angiotensin system and not attributable to other simultaneous actions (on blood pressure, for instance).

None of these evidential needs has been persuasively met at present, although in each case data can be cited both in favour and against the underlying hypothesis.

### Biologically plausible mechanisms

It has long been known that under certain circumstances renin can have deleterious effects upon both the myocardium and vascular tissue. Thus, Asscher and Anson<sup>2</sup> showed that renal extracts produced vascular lesions and effusions which they attributed to a vascular permeability factor. It was subsequently found that angiotensin II infusions mimicked this effect.<sup>3</sup> The specificity of the effect was, however, challenged by the observation that preventing the rise in blood pressure produced by angiotensin II also inhibited the increase in vascular permeability, suggesting that the effect was a mechanical one.<sup>4,5</sup> Mohring and his colleagues challenged this explanation, and in an intriguing group of studies in Goldblatt two-kidney-one-clip hypertension in the rat, they showed that high plasma renin activity concentrations were associated with weight loss and death, while reduction in plasma renin with saline infusion resulted in a remarkable improvement in clinical state and survival.<sup>6</sup> They were, however, unable to discriminate between an adverse effect of sodium and water depletion and increased plasma renin concentrations. It is also noteworthy that two rat models of induced hypertension often accompanied by severe vascular lesions—Goldblatt one-kidney-one-clip and deoxycorticosterone-salt hypertension—are associated with low renin concentrations. Direct effects of angiotensin II on the myocardium were demonstrated by Kremer *et al* who produced extensive focal myocardial necrosis by infusing angiotensin II into rabbits.<sup>7</sup> These lesions were, however, only seen with high angiotensin II concentrations and were probably related to catecholamine

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### Glossary of trials

HAPPHY—Heart attack primary prevention in hypertension  
IPPPSH—International prospective primary prevention study in hypertension  
MAPHY—Metoprolol atherosclerosis prevention in hypertensives study  
SHEP—Systolic hypertension in the elderly programme

induced damage which can produce similar appearances in patients with pheochromocytoma. The lesions are quite distinct from those produced by ischaemic heart disease and therefore probably do not support the theory that there is a link between the renin-angiotensin system and ischaemic heart disease.

The development of inhibitors of the renin-angiotensin system yielded more direct evidence. In experimental preparations, angiotensin converting enzyme (ACE) inhibitors were shown to increase coronary blood flow<sup>8</sup> and to prevent remodelling following experimental myocardial infarction.<sup>9</sup> The latter was associated with prolongation of survival. Although ACE inhibitors improve coronary blood flow in normal subjects,<sup>10</sup> it has been more difficult to demonstrate improvement in coronary blood flow using ACE inhibitors in patients with established coronary heart disease. Such studies do not support the relation between renin and the incidence of coronary events. Further, they do not discriminate between specific direct effects of angiotensin II upon the heart, effects of ACE inhibitors due to other mechanisms such as bradykinin potentiation, or effects of ACE inhibitors due to particularly favourable haemodynamic effects.

Molecular biological techniques have demonstrated persuasively that angiotensin II induces expression of a wide range of genes in vascular tissue. Some of these genes are implicated in atherogenesis and probably mediate the growth effects produced by angiotensin II in vascular smooth muscle cells in tissue culture. (The difficulty in extrapolating such observations to the in vivo situation is that angiotensin II may simultaneously stimulate both proliferative pathways (oncogene expression) and antiproliferative pathways (for example, PDGF-AA and TGF-).)<sup>11</sup> This may explain the observation that in some situations only hypertrophy is produced in vivo, while changing tissue culture media composition may give rise to angiotensin II induced hyperplasia in vitro. In vivo experiments also suggest that angiotensin II can, under some circumstances, have a trophic effect independent of blood pressure. Thus, ACE inhibitors prevented or attenuated the development of myointimal hyperplasia after endothelium denudation in the rat carotid artery.<sup>12</sup> This effect may, however, be due to bradykinin potentiation rather than ACE inhibition.<sup>13</sup> Griffin *et al* showed that resistance vessel hypertrophy induced by angiotensin II was not prevented when the rise in blood pressure was inhibited by the use of hydralazine.<sup>14</sup> However, the haemodynamic effects of hydralazine on pulse pressure may have had an important effect on resistance vessel growth. Harrap *et al* demonstrated persuasively that the regression in resistance vessel hypertrophy produced by ACE inhibitors was completely inhibited when their blood pressure lowering effect was prevented with saline infusion, although in this case, of course, angiotensin II levels remained suppressed or may have been further

reduced.<sup>15</sup> While in some studies ACE inhibitors have been shown to reduce experimental atheroma,<sup>16</sup> such effects have not been carefully distinguished from the haemodynamic effect of these agents. The effects are not observed, for example, with other angiotensin II lowering antihypertensive treatment such as  $\beta$  blockade.<sup>17</sup>

Angiotensin II may play a role in vascular injury mediated by other cytokines. Recently, it has been shown that it increases vascular permeability factor mRNA gene expression in human vascular tissue.<sup>18</sup> It has been associated with increased vascular permeability in diabetes although no direct association with coronary heart disease has yet been shown. Whether this mechanism explains the earlier observations of increased vascular permeability independent of blood pressure changes remains to be seen, but potentially this mechanism is extremely important, although its relevance to ischaemic heart disease is uncertain.

In summary, angiotensin II can in some experimental situations be shown to have a plethora of actions upon vascular tissue. How far these can be related to in vivo mechanisms in man is uncertain until more clinical and experimental studies are conducted.

#### Evidence from association studies

The first evidence that plasma renin was associated with cardiovascular disease came from Laragh's group in New York.<sup>1</sup> Since plasma renin is influenced by sodium intake, they used a nomogram in which plasma renin was plotted against 24 hour sodium excretion in order to increase the sensitivity of the analysis to abnormalities. When a clinic population of 219 patients was examined using the renin profile, it was reported that over a 10 year period none of the 59 patients classified as "low renin hypertension" suffered a heart attack or stroke, while 11% of the 124 patients in the normal plasma renin group and 14% of the 36 patients in the high plasma renin group had suffered one or the other. In a subsequent report based upon 640 patients, the relative protection against heart attack was again observed in the low renin group, but on this occasion strokes were equally distributed.<sup>19</sup>

This type of association study, based upon a referred clinic population, is notoriously subject to systematic error. The renin subgroups were not matched for age, blood pressure, or ethnic origin. The possibility of differential treatment effects in the three groups was not considered. Subsequent clinic based studies yielded divergent results,<sup>20-22</sup> and the prognostic value of "renin profiling" has not been generally accepted.<sup>23</sup> Even if plasma renin values were useful prognostically, this would not necessarily provide support for the view that plasma renin was vasculotoxic. Thus high renin levels could reflect increased sympathetic activity, which itself may be associated with impaired prognosis. Alternatively, increased renin could result from hypertensive vascular damage to the afferent arteriole. Renin levels are usually elevated in malignant

hypertension which would carry a much worse prognosis.<sup>24</sup>

Despite these criticisms, a prospective study partially supports the original observations. Alderman *et al* carried out renin sodium profiling on 1717 hypertensive subjects identified by worksite screening.<sup>25</sup> Subjects were followed for a mean of 8.3 years. The incidence of myocardial infarction per 1000 person-years was 14.7 in high renin hypertensive subjects, 5.6 in normal renin hypertensive subjects, and 2.8 in low renin hypertensive patients. The risk ratio for high versus low renin hypertension was 5.3 (confidence intervals 3.4 to 8.3). Mortality rates showed a similar gradient. A systematic search was carried out for such confounding factors as race, sex, age at entry, serum cholesterol, smoking status, left ventricular hypertrophy, blood glucose, body mass index, history of cardiovascular disease, blood pressure, and use of  $\beta$  blockers, all with negative results. There was no relation between renin profile and the incidence of stroke.

The results from this impressive cohort study are in many ways surprising. Renin status was only classified at entry and must have been profoundly influenced by drug treatment. Nevertheless, initial renin status predicted outcome years later. This must indicate either that the relation between renin and prognosis is an extremely powerful one and persists despite potential dilution from drug treatment or alternatively that plasma renin acts as a marker for ischaemic heart disease by a process quite distinct from direct vascular toxic effects. The failure to demonstrate a relation between renin profile and subsequent stroke suggests that the relation observed in the earlier study was due to an unrecognised confounder.

The only study of similar design from a United Kingdom population does not support the work of Alderman *et al*.<sup>26</sup> Meade *et al* analysed plasma renin activity in a mixed group of hypertensive and normotensive subjects (1999 in total). Twenty four gave a history of previous myocardial infarction and were found to have a lower plasma renin activity than subjects without such a history. This study did not use renin sodium profiling, included a majority of normotensive subjects, and did not examine potential mismatching of renin subgroups for other cardiovascular risk factors: this is particularly important as low renin subjects are likely to be older. A later follow up study by the same group examined outcome in 803 men.<sup>27</sup> Most were normotensive and only 242 were diagnosed as hypertensive. Eighty six first coronary events were observed and there was no relation with plasma renin activity in the group as a whole. There was a weak trend towards increased coronary events in the third of the hypertensive population with highest plasma renin (risk ratio of 1.26, confidence interval 0.63 to 2.56).

The populations investigated are clearly different in these two studies. In both, the number of events was limited and the power to detect genuine associations was correspondingly low. Despite this, the British study was powerful

enough to detect significant effects of cholesterol, body mass index, and systolic blood pressure on the incidence of myocardial infarction. It seems likely, therefore, that if plasma renin has prognostic value, this is at best confined to hypertensive subjects.

One other prospective study by Alderman *et al* bears upon this issue.<sup>28</sup> The group conducted a study in which 2937 hypertensive subjects were followed for an average of 3.8 years. In a Cox multivariate analysis, log plasma renin activity together with age, systolic blood pressure, and cholesterol was directly associated with the incidence of myocardial infarction, whereas urinary sodium was inversely associated with incidence of myocardial infarction (that is, higher sodium intakes appeared to carry a protective effect). Interestingly, when plasma renin activity was excluded from the multiple regression model, the sodium-myocardial infarction association became substantially stronger. On the other hand, when plasma renin activity as well as sodium were included, both associations remained significant, indicating that the relation of the two with myocardial infarction was partially independent. The presence of apparent associations when renin sodium profiling is used, together with these observations, suggest that high plasma renin activity is not acting as an indicator of suboptimal sodium intake.

In conclusion, these association studies do not provide consistent evidence for a renin-coronary heart disease relation. Even where it has been shown, the possibility remains that it is attributable to unrecognised confounding factors, and the failure of treatment to eliminate a putative relationship at recruitment to these studies remains puzzling.

### Intervention trials

The gold standard design for demonstrating a causal role for circulating renin in coronary heart disease would be an intervention trial in which specific inhibition of the renin-angiotensin system protected susceptible patients against ischaemic heart disease. Such studies are not available. There are, however, several trials which do indirectly shed light upon this hypothesis. There are three types: (1) studies in which the incidence of coronary heart disease has been examined when blood pressure is lowered by manoeuvres which either stimulate or reduce plasma renin levels; (2) studies in which the impact of more specific inhibition of the renin-angiotensin system has been examined in heart failure patients who are at high risk of recurrent myocardial infarction; and (3) comparative trials using vascular remodelling as a surrogate end point for coronary heart disease.

#### INTERVENTION TRIALS IN HYPERTENSION

In some trials which have examined the impact of antihypertensive treatment on cardiovascular endpoints, treatments which stimulate and reduce circulating renin have been used. In the Medical Research Council (MRC) trial in mild hypertension, patients

were randomly allocated to bendrofluazide, propranolol, or placebo.<sup>29</sup> The results were diluted by the need to use second line treatments in substantial numbers of patients. However, the high doses of bendrofluazide used (10 mg/d) would be expected to raise plasma renin while propranolol would be expected to reduce it. Strokes were significantly reduced from a placebo rate of 2.6 per 1000 person-years of observation to 0.8 per 1000 person-years of observation in the bendrofluazide group, but not significantly reduced in the propranolol group (1.9 per 1000 person-years). Coronary events were not significantly reduced in either group (5.6 per 1000 person-years on bendrofluazide, 4.8 on propranolol, and 5.4 on placebo). Neither of these findings, therefore, supports the hypothesis that induced changes in plasma renin influence the incidence of stroke or heart attack independently of changes in blood pressure. Only if total infarction rates (that is, silent plus clinical infarctions) are taken into account did the propranolol group fare significantly better when compared with the bendrofluazide treated group. In the MRC trial of treatment in older adults, patients were randomised to atenolol or a hydrochlorothiazide-amiloride combination.<sup>30</sup> The diuretic group showed significantly reduced risks of stroke (31%), coronary events (44%), and all cardiovascular events (35%) compared with placebo. There were no significant reductions in the incidence of any of these three primary end points in the  $\beta$  blocker group; the difference between diuretic and  $\beta$  blocker groups was statistically significant in each case.

Two other trials have attempted to detect preferential effects of  $\beta$  blockers on coronary events in the treatment of hypertension: the HAPPHY<sup>31</sup> and IPPPSH trials.<sup>32</sup> Neither detected any significant reduction in coronary heart disease in the  $\beta$  blocker treated group, although this therapy would have been expected to lower renin levels. In both cases, however, additional drug treatment may have complicated the issue. Only when the HAPPHY trial was extended as the MAPHY trial was there a significantly lower mortality from myocardial infarction in the metoprolol treated group compared with those who received diuretics.<sup>33</sup>  $\beta$  Blockade clearly has an impact on cardiac disease quite distinct from any putative effect of renin lowering, and the interpretation of these results in the present context is therefore debatable. However, it seems clear that in some patient groups (particularly the elderly), treatment which raises renin concentrations has a major impact upon coronary heart disease of the approximate order of the epidemiological risk. The 27% reduction in myocardial infarction in the SHEP trial, which used chlorthalidone as first line treatment, is consistent with this.<sup>34</sup>

**Trials in congestive cardiac failure**

ACE inhibitors have been shown to improve both morbidity and mortality in patients with left ventricular dysfunction.<sup>35 36</sup> In some of

these trials there has been an unexpected but significant reduction in recurrent myocardial infarction. In one large trial, however, no reduction was observed.<sup>37</sup> How far favourable effects are attributable to a specific effect upon circulating angiotensin II and how far they are attributable to a particularly favourable haemodynamic effect is uncertain, and findings in this very special situation cannot reasonably be extrapolated to primary prevention studies.

*Effect of ACE inhibitors on vascular remodelling*  
Hypertension is associated with an increased wall to lumen ratio in the resistance vessel.<sup>38</sup> This is mainly or wholly due to rearrangement of the media resulting in a reduction of luminal diameter without any increase in mass. The mechanism of this effect is unknown. Two studies have compared ACE inhibition with  $\beta$  blockade and both have found that chronic treatment with ACE inhibitors reverses vascular remodelling in subcutaneous resistance vessels while  $\beta$  blockade does not.<sup>39 40</sup> Although this has been attributed to specific effects of angiotensin II upon the vasculature, this interpretation is not particularly persuasive, as  $\beta$  blockade would also be associated with some reduction in angiotensin II, although probably not to the same extent as ACE inhibitors. In addition, vascular remodelling represents a fundamentally different pathological process from coronary atheroma, and the relevance of these findings is doubtful; however, if coronary vessels underwent similar remodelling, potential effects on coronary flow reserve might be of importance.

**Conclusion**

There is no consistent body of evidence to implicate circulating renin independently of blood pressure in the pathogenesis of coronary events (table). Although some data are impressive, they are all controversial, with divergence both in epidemiology and trial results. Likewise, biological events triggered by angiotensin II are complex and opposing processes are stimulated in vitro, making in vivo prediction impossible. The development of more specific inhibitors of the renin-

*Evidence implicating renin in pathogenesis of coronary events*

| Evidence             | Conclusions   |
|----------------------|---|
| Biological processes | <ul style="list-style-type: none"><li>● In vitro evidence for and against</li><li>● Experimental models—no consistent support</li></ul>   |
| Association studies  | <ul style="list-style-type: none"><li>● Retrospective clinic based studies conflicting, and of dubious value</li><li>● Prospective studies: positive in two groups of hypertensives</li><li>● Negative in population study</li></ul>  |
| Intervention studies | <ul style="list-style-type: none"><li>● None directly addressing the issue</li><li>● Little evidence that renin stimulating treatment increases incidence of ischaemic heart disease</li><li>● ACE blockade in patients with left ventricular dysfunction mainly supportive, but impossible to exclude haemodynamic effects</li><li>● Effect of ACE blockade on vascular remodelling supportive, but of dubious relevance</li></ul> |

angiotensin system may make the hypothesis easier to test, although the need for end point trials makes such investigation complex and expensive. At present there is insufficient persuasive evidence to render this hypothesis relevant in treating individual patients.

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